

Adenomas as a risk factor in familial colorectal cancer: implications for screening and surveillance in the UK

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Abstract

Colorectal cancer (CRC) develops in a step-wise fashion from a normal epithelium, through dysplastic adenomas into invasive carcinoma. In addition to familial adenomatous polyposis and Lynch syndrome, approximately 10-35% of CRCs are familial in nature. CRC screening and surveillance programs are based on an understanding of polyp natural history and rely on the ability to endoscopically remove pre-malignant lesions before they are capable of developing invasion. There are however significant differences in these guidelines between the United Kingdom (UK) and the United States of America, in relation to the weight attributed to a family history of polyps. Here we show using publicly available national datasets that these guideline differences unexpectedly generate inadequate screening recommendations for second-degree relatives of patients with CRC in the UK. We validate our simple mathematical modelling of the clinical problem on a regional dataset as well as previously published study data to demonstrate correct interpretation. We further discuss the implications of a family history of adenomas in the contemporary climate of the Bowel Cancer Screening Program and suggest a re-evaluation of the UK guidelines in light of this developing issue.

What does this paper add?

This paper, using simplistic mathematical modelling, describes a clinical problem driven through national differences in endoscopy guidelines that results in inappropriate screening of kindred of those with CRC. The consequences of these differences are a number of preventable cancers occurring every year in the UK.

The lifetime risk for colorectal cancer (CRC) is more than trebled for first-degree relatives (FDRs) of patients with CRC [1]. Although there are well-defined syndromes for some forms of familial CRC such as familial adenomatous polyposis (FAP) and hereditary non-polyposis colorectal cancer (HNPCC), there exist many molecularly undefined, although still familial, alternative forms of CRC that are reported to account for between 10-35% of CRC cases [2, 3]. There are now population-wide clinical guidelines that not only can estimate an individual's risk for developing CRC but also guide screening and surveillance decisions. Patients found to have an increased risk for CRC, in relation to family history, are generally offered further investigations, the gold-standard being colonoscopy. The advantages of colonoscopy over alternative radiological investigations such as CT colonography are its combined diagnostic and therapeutic benefits. Although improvements in molecular stratification have identified many more numerous subtypes of CRC than previously thought with different driver mutations or gene expression profiles, it remains generally accepted that the majority of CRCs still develop in the classical Vogelstein manner. Typically, this is described as a sequential acquisition of oncogenic events and loss of tumour suppressor activity, phenotypically characterised by the development of dysplastic adenomas and then invasive carcinoma from normal epithelium [4]. Thus, the oncological benefit in the endoscopic removal of pre-malignant adenomas is clear and well described, in that it prevents the development of invasive carcinoma which would otherwise require the patient to undergo surgical colectomy with possible adjuvant therapy.

In the UK and the USA clinical guidelines linking endoscopic screening to family history differ in relation to the risk attributable to a family history of colorectal adenomas [5, 6]. In the UK, a family history of adenomas does not form part of the guidelines; whereas in the USA adenomas are identified as an independent risk factor requiring surveillance in relatives. Whilst there are health economic issues to take into account relative to the benefit of including a family history of adenoma in screening guidelines, these differences generate some hidden potential clinical decision making pitfalls for individual patients. We have previously shown, in a district general hospital setting, that patients undergoing polypectomy, who have a family history of CRC, although diminishing their own chances of developing CRC, paradoxically change the subsequent guidance recommendations for their off-spring [7]. The unintended effect of this altered risk calculation for the second-degree relatives (SDR) is that these patients would no longer be offered surveillance under current guidelines despite their own individual risk not having changed (Figure 1). Here, we validate these local results, using publicly available data sets, at a population level using conservative estimates of burden.

There are on average 41581 cases of CRC per annum in the UK of which 4158 will be familial, assuming only 10% of cases are familial in origin [8]. The lifetime risk of developing cancer in an individual who is a FDR of a patient with CRC is approximately 9% [9]. The Office for National Statistics states that on average there are 1.7 (2) children per family [10]. If each familial case therefore had two children and all these FDRs were identified as being at risk and offered colonoscopy then $748 (2 \times (4158 \times 0.09))$ potential cancers could be prevented by prophylactic polypectomy. The FDRs inherited risk for CRC however remains unchanged although they would not have developed CRC. Next, if all these FDRs subsequently have a further 2 children each (1497) then these SDRs' management will be different according to whether they live in the UK or the USA. In the UK, their parental adenomas will not be classified by current guidelines as a risk factor and the SDR will not be offered surveillance. In the USA however they would be offered surveillance based on the family history of adenomas alone. Thus, theoretically in the UK, 135 patients per annum of these second-degree relatives (1497×0.09) could go on to develop familial inherited CRC through inadequate surveillance despite having a bona fide family history.

In order to validate this highly simplistic and conservative national population model we applied the same approach to the region we had previously carried out our pilot study in: Cheltenham and Gloucester NHS Trust (C&G). C&G serves a population of 612,000 equating to roughly 0.9% of the UK population. C&G sees approximately 375 cases of CRC per annum. Again, assuming 10% of these will be familial (38) then this will lead to 76 'at-risk' FDRs. If these patients all undergo surveillance endoscopy then this should lead to 6.84 (7) cases of prevented cancers per annum. In our previously published work we identified 14 such cases over an 18 month period (i.e. 9 per annum); a not dissimilar number to that which our model predicts.

These relatively simplistic calculations validate our approach, showing it can calculate the rough numbers of patients at-risk of developing CRC through inadequate surveillance in the UK following current guidelines. The calculated annual burden in the UK of this clinical problem is low - 135 per annum or 0.3% of total CRC numbers; although these are entirely avoidable deaths. Given the small size of the problem however any form of prospective study to identify statistically different numbers of CRCs prevented as a result of a change to the current screening guidelines are unfeasible both in time and scale.

From a health economic perspective, the NHS tariff for an adult diagnostic colonoscopy is £446 and for an uncomplicated colectomy around £5700. From our calculations, the additional financial burden of endoscopy would be £668K (1497×446) whereas the cost without screening, assuming 135 patients would subsequently develop cancer, of the surgery alone (excluding

radiological/endoscopic diagnosis +/- chemotherapy) equates to near £770K. Further, given the relatively small numbers of additional patients requiring colonoscopy per hospital we believe that this would have a negligible effect on already stretched endoscopy departments.

Our estimation of the size of the clinical problem uses a conservative value of familial CRC incidence (10%). If the same calculations are performed using the higher end quoted incidence (35%) then the number of avoidable CRC cases per annum reaches 472, with an associated endoscopy cost of ~£2.4M with screening compared to the surgical cost *per se* of ~£2.7M without screening. These calculations confirm that even without an exact knowledge of the incidence of familial CRC, taking both higher and lower published estimates, screening these at-risk patients makes clinical and economical sense.

Our description of the current clinical problem of missed-kindred screening, will inevitably get worse somewhat with time, partly as a result of the bowel cancer screening program. As the current program embeds and increasing numbers of cancers are 'prevented' by polypectomy with subsequent surveillance, those with non-classical (i.e. non-HNPCC/FAP) familial pre-disposition to cancer will no longer develop cancer, rather polyps alone. However, their genetic/epigenetic CRC predisposition will still be transferred to a proportion of their children. If the current guidelines are not changed we will see increasing numbers of these 'at-risk' FDRs also not being offered surveillance and many will inevitably develop CRC in a manner analogous to the current smaller scale SDR problem we describe earlier.

We believe that we have demonstrated a hitherto under-appreciation of a small but entirely preventable clinical problem that has arisen fundamentally as a result of family history screening guidelines in the UK. Perhaps, the bigger question to discuss as a community is whether a family history of polyps *per se* should be recognised, as per the US guidelines, as an independent risk factor for CRC. There are a large number of studies in the literature demonstrating the additional risk posed by a family history of colorectal polyps. A meta-analysis published in 2001 based on 9 independent studies showed that the presence of an adenoma in a FDR generates an estimated relative risk (RR) of 1.99 (95% CI=1.55-2.55) for the individual [11]. Further, the authors also identified an association between age at when the adenoma was diagnosed and the RR; with an even higher RR in a FDR whose relative was diagnosed with adenomas at a young age (≤ 60 y). A more recent large-scale retrospective case-control study from the USA looked at the risk of adenomas and CRC in FDRs, as well as SDRs and third-degree relatives (TDR) of patients with an adenoma or advanced adenoma [12]. This study convincingly demonstrates that FDRs, SDRs and TDRs of those with either adenomas or advanced adenomas have a higher risk of developing either

CRC or adenomas. These recent data are in support of several other older studies showing similar findings [13-16].

The implications of these studies are that FDRs of those with adenomas should be offered endoscopic screening. This has significant clinical, economic and logistical implications. The morbidity of colonoscopy whilst small is not insignificant: intestinal perforation (1:1,000), bleeding (1:200) as well as bowel preparation related renal complications [17]. Indeed, these are certainly underestimates as this population group will more likely than chance require polypectomy due to their enhanced risk. Further, a proportion of these patients will inevitably require elective operative intervention for CRC or non-endoscopically resectable polyps with all the associated risks of complications and death (2-4%). Whilst the enhanced screening protocol proposed could decrease the number of patients presenting with more advanced CRC whether this would diminish overall mortality rather than disease-specific mortality is moot, topical and relevant [18].

The increased economic burden of colonoscopic screening in FDRs of those with adenomas would be huge given the prevalence of adenomas in the average risk patient equates to ~30% [19]. In addition to cost, the logistics of organising this in an IT-fragmented NHS will inevitably lead to missed cases or inappropriate intervention. It follows that there will be a reliance on the patient having an in-depth knowledge of their relatives' colonoscopy findings and histology in order, for example, to distinguish hyperplastic from dysplastic polyps. There is good evidence that both patients and relatives have poor recall of these important data which will further complicate the process [20, 21]. Finally, there would be the issue of when to start screening in FDRs of those with adenomas. Recent scientific advances propose that not all polyps are alike, for example sessile serrated polyps are generally over-represented by BRAF mutations. The variable molecular landscape of these early lesions translates into different biological behaviour so in the future in addition to molecular stratification of CRCs there will be a need for a similar understanding of adenomas to guide both the patient's surveillance and the timing of the FDRs initial colonoscopy. Although clearly challenging, we feel these concepts need open discussion, to at least help inform consultations with individual patients. At the very minimum we feel that the presence of a family history of polyps should prompt inquiry into a history of CRC in the preceding generation and that these patients should be offered endoscopic screening on a case-by-case basis.

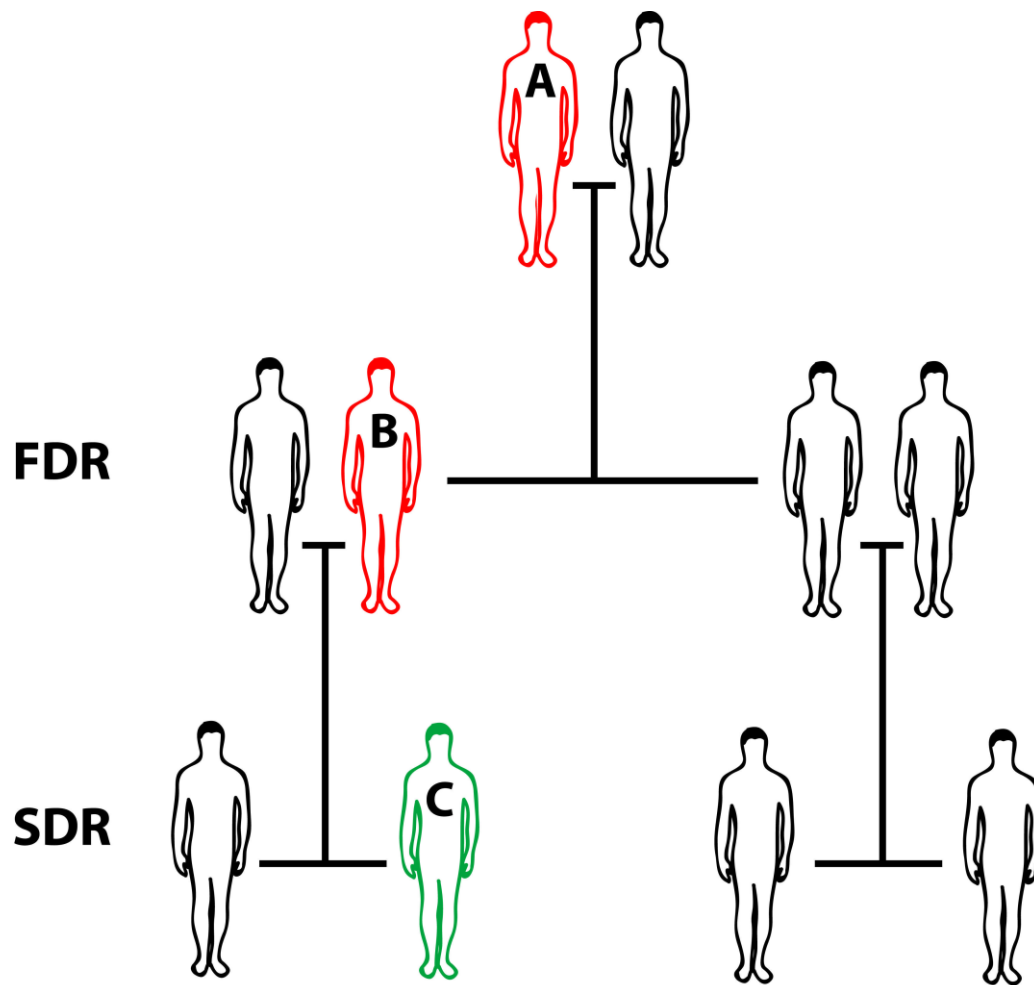


Figure 1. Schematic representing the concept of inadequate screening in second-degree relatives of patients with colorectal cancer

Index patient (A) is diagnosed with familial colorectal cancer, as such the FDRs undergo colonoscopic screening. Case (B) inherits the parental predisposition to CRC but as a result of the colonoscopy has polyps removed. SDR (C) of the index case (A) also inherits the cancer predisposition from parent (B) but because parent (B) only progressed so far as to developing polyps is not offered screening and as such goes onto develop CRC.

REFERENCES

1. Butterworth AS, Higgins JP, Pharoah P. Relative and absolute risk of colorectal cancer for individuals with a family history: a meta-analysis. *European journal of cancer*. 2006;42(2):216-27.
2. Burt RW. Colon cancer screening. *Gastroenterology*. 2000;119(3):837-53.
3. Lichtenstein P, Holm NV, Verkasalo PK, Iliadou A, Kaprio J, Koskenvuo M, et al. Environmental and heritable factors in the causation of cancer--analyses of cohorts of twins from Sweden, Denmark, and Finland. *The New England journal of medicine*. 2000;343(2):78-85.
4. Vogelstein B, Fearon ER, Hamilton SR, Kern SE, Preisinger AC, Leppert M, et al. Genetic alterations during colorectal-tumor development. *The New England journal of medicine*. 1988;319(9):525-32.
5. Cairns SR, Scholefield JH, Steele RJ, Dunlop MG, Thomas HJ, Evans GD, et al. Guidelines for colorectal cancer screening and surveillance in moderate and high risk groups (update from 2002). *Gut*. 2010;59(5):666-89.
6. Levin B, Lieberman DA, McFarland B, Andrews KS, Brooks D, Bond J, et al. Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: a joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. *Gastroenterology*. 2008;134(5):1570-95.
7. Vaughan-Shaw PG, Borley NR, Tomlinson IP, Wheeler JM. Polypectomy in patients with a family history of colorectal cancer may lead to inadequate surveillance and missed cancers in their kindred. *Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland*. 2013;15(11):1452-3.
8. Cancer Research UK. 2015. Available from: <http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/bowel-cancer>.
9. Surveillance Epidemiology and End Results Database. (www.seer.cancer.gov/popdata), National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released January 2015.
10. Office for National Statistics. 2012. Available from: www.ons.gov.uk.
11. Johns LE, Houlston RS. A systematic review and meta-analysis of familial colorectal cancer risk. *The American journal of gastroenterology*. 2001;96(10):2992-3003.
12. Tuohy TM, Rowe KG, Mineau GP, Pimentel R, Burt RW, Samadder NJ. Risk of colorectal cancer and adenomas in the families of patients with adenomas: a population-based study in Utah. *Cancer*. 2014;120(1):35-42.

13. Cottet V, Pariente A, Nalet B, Lafon J, Milan C, Olschwang S, et al. Colonoscopic screening of first-degree relatives of patients with large adenomas: increased risk of colorectal tumors. *Gastroenterology*. 2007;133(4):1086-92.
14. Gupta A, Samadder J, Elliott E, Sethi S, Schoenfeld P. Prevalence of adenomas and advanced adenomas in patients in the 40- to 49-year age group undergoing screening colonoscopy because of a family history of adenoma/polyp in a first-degree relative. *Gastrointestinal endoscopy*. 2012;75(4):705-11.
15. Lynch KL, Ahnen DJ, Byers T, Weiss DG, Lieberman DA. First-degree relatives of patients with advanced colorectal adenomas have an increased prevalence of colorectal cancer. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association*. 2003;1(2):96-102.
16. Pariente A, Milan C, Lafon J, Faivre J. Colonoscopic screening in first-degree relatives of patients with 'sporadic' colorectal cancer: a case-control study. *The Association Nationale des Gastroenterologues des Hopitaux and Registre Bourguignon des Cancers Digestifs (INSERM CRI 9505)*. *Gastroenterology*. 1998;115(1):7-12.
17. Ko CW, Dominitz JA. Complications of colonoscopy: magnitude and management. *Gastrointest Endosc Clin N Am*. 2010;20(4):659-71.
18. Prasad V, Lenzer J, Newman DH. Why cancer screening has never been shown to "save lives"-and what we can do about it. *BMJ*. 2016;352:h6080.
19. Heitman SJ, Ronksley PE, Hilsden RJ, Manns BJ, Rostom A, Hemmelgarn BR. Prevalence of adenomas and colorectal cancer in average risk individuals: a systematic review and meta-analysis. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association*. 2009;7(12):1272-8.
20. Elias PS, Romagnuolo J, Hoffman B. Poor patient knowledge regarding family history of colon polyps: implications for the feasibility of stratified screening recommendations. *Gastrointestinal endoscopy*. 2012;75(3):598-603.
21. Kumaravel V, Heald B, Lopez R, Hasson H, Schneider K, Burke CA. Patients do not recall important details about polyps, required for colorectal cancer prevention. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association*. 2013;11(5):543-7 e1-2.